UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OCT 11 1990

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Uniconazole

FROM: Joycelyn Stewart, Ph.D. 9/19/90
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

and

George Z. Ghali, Ph.D. G.Ghali 9.20.90
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division (HED) Peer Review Committee met on July 25, 1990 to discuss and evaluate the weight-of-the-evidence on Uniconazole with special reference to its carcinogenic potential. Based on all information available, the Committee concluded that Uniconazole should be placed in Group C, possible human carcinogen. This classification was based upon increased incidence of hepatocellular adenomas, carcinomas and adenomas/carcinomas combined in male CD-1 mice. Quantification of potential human cancer risk, using the low dose extrapolation model ($Q1^*$) was not recommended. Therefore, the Reference Dose (RfD) approach will be used for the quantification of potential human risk.

A. Individuals in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated.)

Penelope A. Fenner-Crisp
Reto Engler
Karl Baetcke
John Quest
Marcia van Gemert
Marion Copley
Esther Rinde
William Sette
Yin-Tak Woo
Hugh Pettigrew
George Ghali

2. Peer Review Members in Absentia (Those unable to attend the discussions; signature indicates concurrence with overall conclusions of the Committee.)

William Burnam
Kerry Dearfield
Richard Hill
Robert Beliles
Julie Du

3. Scientific Reviewers (Noncommittee members responsible for presentation of data; signature indicates technical accuracy of panel report.)

Joycelyn Stewart
Bernice Fisher

4. Other attendees

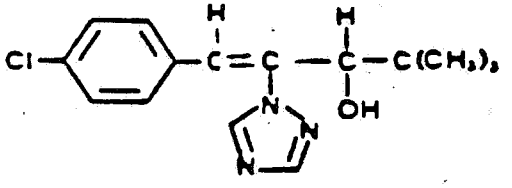
Linda Kutney and Flora Chow of SACB, HED.

B. Material Reviewed

The material available included Data Evaluation Records (DERs) of the mouse oncogenicity feeding study and the rat chronic toxicity/oncogenicity feeding study. There were also summaries of other relevant toxicology information prepared by Dr. J. Stewart and a qualitative risk assessment for the oncogenicity study in CD-1 mice prepared by Dr. H. Pettigrew.

C. Background Information

Uniconazole* [(E)-(s)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-yl)-pent 1-ene-3-ol] is a new chemical manufactured by Valent U.S.A. Corporation proposed for use as a plant growth regulator on non-food crops.



Uniconazole

The chemical is formulated in two end-use products: Prunit (2.5% ai) which is applied to trees by injection and Sumagic (0.05% ai) which is used as a foliar spray on greenhouse-grown ornamental crops.

D. Evaluation of Carcinogenicity Evidence

1. Morseth, S.L. (1989) Oncogenicity Study in Mice with S-3307D. Unpublished report prepared by Hazleton Laboratories America, Inc., Report No. HLA 343-190-CIT, dated May 4, 1989. MRID No. 411620-05.

   a. Experimental Design - Technical Uniconazole was administered in the diet to 80/sex of Crl:CD-1 mice at doses of 0, 10, 40, 200, and 1500 ppm for 78 weeks (approximately equivalent to 0, 1.5, 6, 30, and 225 mg/kg/day). Fifty animals/sex/group were used in the main study, while the remainder were used in a satellite study. Ten/sex/group of the satellite animals were bled for hematology and sacrificed at 52 weeks. The remaining 20/sex/group were carried to study termination at 78 weeks, but were not included in the pathology report.

   b. General Observations and Mortality - There was no effect of treatment on clinical signs, mean body weight, food consumption, water consumption, or hematology. Mortality was decreased in the high-dose male mice when compared to the controls, with a significant negative trend ($p < 0.01$). In addition, pairwise comparison between the high-dose males and the other treated groups resulted in statistically significant decreases in mortality in the high-dose group. There were no significant survival disparities among female groups (Table 1).

Table 1. Uniconazole-P CD-1 Mouse Study, Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Week				
Dose (ppm)	1-26	27-52	53-78	79-81[a]	Total
0	1/49	4/48	21/44	4/23	30/49 (61) n**
10	0/50	1/50	21/49	1/28	23/50 (46)
40	0/50	2/50	23/48	0/25	25/50 (50
200	0/50	0/50	22/50	0/28	22/50 (44)
1500	0/50	0/50	11/50	1/39	12/50 (24) n**

[+]Number of animals that died during interval/number of animals alive at the beginning of the interval.
() = percent.
[a]Final sacrifices at weeks 80-81.
[n]Decreasing trend or negative change from control.
* = $p < 0.05$, ** = $p < 0.01$.
Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.

c. Consideration of the Adequacy of Dose Selection - The high dose tested was considered adequate for carcinogenicity testing although it appears that females could have tolerated higher dosage.

In high-dose males, weight gain in weeks 1 to 13 was 10.8 percent lower than in the controls in the main study. A similar effect was not seen in the high-dose males of the satellite animals, or in high-dose females of either the main or satellite studies.

Absolute and relative mean liver/gallbladder weights were increased significantly in high-dose male and female mice, both at the 52-week sacrifice and at the terminal sacrifice. At the 52-week sacrifice, the liver weight increases were as follows: males 58.6 and 50.8 percent; females 38.7 and 43.0 percent. At terminal sacrifice, the increases were: males, 51.3 and 58.9 percent; females 38.2 and 34.3 percent, respectively.

The doses for the 18-month mouse study were selected based on results obtained in a 5-week dietary study conducted in Crl:CD mice at doses of 0, 100, 300, 1000, 3000, and 10,000 ppm, approximately equal to 0, 15, 45, 150, 450, and 1500 mg/kg/day. In that study, the following results were reported: 5/12 high-dose females died or were sacrificed moribund; and hematocrit, hemoglobin, erythrocytes, platelets, lymphocytes, body weight and body weight gain were reduced in high-dose male and female mice. Body weight was reduced 26 and 24 percent in high-dose male and female mice. SGOT, SGPT, and alkaline phosphatase, absolute and relative liver/gallbladder weights were significantly increased in 1000, 3000, and 10,000 ppm animals. Liver weights were increased 28, 48, and 60 percent in males and 21, 42, and 62 percent in females in the 1000, 3000, and 10,000 ppm groups, respectively. Microscopically, livers showed hepatocellular enlargement, fatty changes, and focal and individual cell necrosis at 1000 ppm and above.

d. Non-Neoplastic Lesions - On gross examination, enlarged livers and liver masses were seen in high-dose groups both at the 52-week sacrifice time and at the terminal sacrifice at 78 weeks. These lesions were seen in more male than female mice.

Non-neoplastic lesions were mainly seen in the liver, and consisted of diffuse hepatocellular enlargement and vacuolation, hepatocellular necrosis, focal chronic inflammation, and pigmented macrophages. Hepatocellular enlargement was seen in all high-dose male and female mice sacrificed at 52 weeks. These lesions also were seen in animals sacrificed moribund and in those sacrificed at study termination. Amyloid deposition was present in nearly all organs in the mice in the study, including the controls. The most frequently observed non-neoplastic lesions are shown in Table 2.

e. Neoplastic Lesions - There was a statistically significant increase in hepatocellular adenomas, carcinomas, and adenomas/ carcinomas combined in high-dose male mice when compared to controls, with statistically significant increasing positive trends. The incidence of hepatocellular tumors was similar in control and treated female mice. There were no other neoplastic lesions attributable to administration of Uniconazole. The incidence of liver tumors observed in the study is shown in Table 3.

The incidence of hepatocellular adenomas ~~were~~ was outside the historical control range for this type of lesion in CD-1 mice (range 0.0-15% with an average of 8.8%). However, the incidence of hepatocellular carcinomas was within the historical control range for this type of lesion for this strain of mice (range 0.0-13.5% with an average of 5%). The historical control data were generated in the same testing facilities between 1985 and the present.

Table 2. Selected Non-Neoplastic Findings for Liver and Other Organs in Mice Fed Uniconazole-P for 78 Weeks

	Dietary Level (ppm)									
	Males					Females				
Organ/Finding	0	10	40	200	1500	0	10	40	200	1500
Liver	(50)[a]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Diffuse hepatocellular enlargement	2	0	0	0	50	0	0	0	0	50
Diffuse hepatocellular vacuolization	3	0	1	0	17	1	2	2	0	18
Focal chronic inflammation	35	39	41	39	50	44	44	42	44	46
Focal necrosis	8	6	8	5	15	6	9	8	6	10
Pigmented macrophages	10	17	18	15	46	23	23	12	16	37
Kidney	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Foci of mononuclear cell infiltration	49	46	48	45	47	47	44	42	44	46
Nephropathy, chronic progressive	42	39	39	43	45	34	38	38	39	44
Lung	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Perivascular/ peribronchial lymphoid hyperplasia	43	39	43	41	47	44	40	41	42	47
Adrenal Cortex	(50)	(25)	(25)	(22)	(50)	(50)	(22)	(22)	(19)	(49)
Hyperplasia, subcapsular cell	31	8	13	7	22	44	16	17	17	48
Urinary Bladder	(50)	(25)	(25)	(22)	(50)	(50)	(22)	(22)	(10)	(49)
Foci of mononuclear cell infiltration, submucosal	14	5	6	1	13	15	4	8	5	18
Testis	(50)	(23)	(26)	(24)	(50)	(0)	(0)	(0)	(0)	(0)
Hypospermia	26	17	17	21	40	0	0	0	0	0

[a]Numbers in parentheses represent the numbers of animals with tissues examined.

Table 3. Male Hepatocellular Tumor Rates[+] and Peto's Prevalence Test Results

Tumor	Dose (ppm) 0	10	40	200	1500
Liver Adenomas	4/41 (9)	6[a]/40 (15)	3/35 (7)	8/38 (21)	14/49 (29)
p =	0.011**				0.029*
Liver Carcinomas	1/43 (2)	1/43 (2)	2/47 (4)	1[b]/45 (2)	6/49 (12)
p =	0.005**				0.019*
Both	5/43 (12)	7/43 (16)	5/47 (11)	9/45 (20)	17/49 (35)
p =	0.004**				0.017*

[+]Number of tumor-bearing animals/number of animals examined, excluding those that died before observation of the first tumor.
() = percent.
[a]First liver adenoma observed at week 69, dose 10 ppm.
[b]First liver carcinoma observed at week 61, dose 200 ppm.
* = $p < 0.05$.
** = $p < 0.01$.

Significance of trend denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.

2. Morseth, S.L. (1989) Combined Chronic Toxicity and Oncogenicity Study in Rats with S-3307D. An unpublished report prepared by Hazleton Laboratories, Inc., Report No. HLA 343-191, MRID No. 411620-06.

   a. Experimental Design - Uniconazole 98.3 percent active ingredient was administered in the diet to 50/group male and female Crl:CD(BR)SD rats for 104 weeks, and to 40/group of the same strain rats for 53 weeks at dosage levels of 0, 10, 40, 200, and 1000 ppm. These doses were approximately equivalent to 0, 0.5, 2.0, 10, and 50 mg/kg/day. Ten/sex/group of the satellite animals were bled for hematological examination, while 10/sex were bled for clinical chemistry analysis. Urinalyses were performed on 20 rats/sex/group at 13, 26, 53, 78, and 104 weeks.

   b. General Observations and Mortality - Survival was unaffected by administration of the test compound. No effects of biological significance on hematological parameters were seen in rats administered Uniconazole. Treatment-related clinical chemistry alterations were as follows: total cholesterol levels were significantly increased in females but not males receiving 1000 ppm at all reporting periods; triglyceride levels were increased in high-dose males when compared to controls, but were significant only at week 13; triglyceride levels were significantly increased in high-dose females at week 26. A decreased incidence and severity of occult blood in the urine in male rats receiving 1000 ppm was reported at all reporting periods. The significance of the decrease is unknown. No other effects of toxicological importance were seen.

      In animals of the main group, mean body weights were decreased significantly ($p < 0.05$) in males and females at all reporting periods up to week 104. Mean body weight gains were decreased by more than 10 percent in males and females receiving 1000 ppm at weeks 0 to 13, 0 to 26, 0 to 38, 0 to 50, and 0 to 78 when compared to their respective controls. The total decrement in body weight gain over the 104 study weeks was 13 percent for male rats and 14 percent in female rats, respectively. In the satellite group, males and females receiving 1000 ppm had significantly lower body weights at weeks 13, 26, 38, and 50 when compared

to controls. Mean body weight gains were significantly lower for males receiving 1000 ppm at weeks 0 to 13. No treatment-related effects were seen on food consumption.

In the satellite animals sacrificed at 52 weeks, absolute and relative (to body weight) liver weights of high-dose male and female rats were significantly increased (25, 22, 19, and 28) percent, respectively) as compared to controls. After 104 weeks of treatment, absolute and relative liver weights of high-dose male and female rats were significantly higher than those of controls ($p < 0.05$).

In high-dose males and females, liver weights were increased 22 and 15 percent, respectively, when compared to control rats. No gross lesions were demonstrated which could be attributed to administration of Uniconazole.

In the animals sacrificed at 52 weeks, male and female rats receiving 1000 ppm exhibited increased incidences of hepatocellular enlargement and vacuolation. Necrosis of individual hepatocytes was reported in 3/10 males and 5/10 females. Except for the necrosis, similar non-neoplastic lesions were seen in high-dose animals sacrificed at 104 weeks. The incidence of non-neoplastic lesions observed in animals in the main study is shown in Table 4. No neoplastic lesions attributable to administration of the test chemical were noted in male or female rats.

The systemic NOEL was 200 ppm, equivalent to 10 mg/kg/day, and the LOEL was 1000 ppm, based on decreased body weights, increased liver weights, and liver lesions.

c. Consideration of Adequacy of Dose Selection - The study was conducted at adequate doses, as indicated by decreased body weight gains (> 10%) in male and female high-dose rats.

The doses used in the carcinogenicity study were determined from a 90-day feeding study in CD SD rats. In the 90-day study, Uniconazole was administered in the diet at doses of 0, 30, 100, 1000, and 3000 ppm.

Mean body weights were depressed in males (8 and 15%) and females (14 and 16%) fed 1000 and 3000 ppm, respectively, throughout the study. No significant effects of compound administration were seen on total food consumption. Hemoglobin, hematocrit, and erythrocytes were reduced in 1000 ppm males and in 3000 ppm females. Male rats receiving 1000 and 3000 ppm had decreased platelet counts, and those receiving 3000 ppm had reduced total leukocyte counts. Serum SGOT was increased in high-dose males, while serum SGPT was increased in those receiving 1000 and 3000 ppm. Cholesterol and phospholipids were increased in females receiving 1000 and 3000 ppm. Liver weights were significantly increased in males and females receiving 1000 and 3000 ppm, and thyroid weights were increased in males receiving 3000 ppm. These were correlated with cloudy swelling of the liver, and increased incidence of small follicles and cytoplasmic vacuolation of the thyroid gland.

d. Non-Neoplastic Lesions - Table 4 illustrates the most frequently observed non-neoplastic lesions in the liver and testes.

e. Neoplastic Lesions - Treatment did not alter the spontaneous tumor profile for this strain of rats.

Table 4. Representative Non-Neoplastic Findings in Rats Fed Uniconazole for 104 Weeks[a]

Organ/Finding	Dietary Level (ppm)									
	Males					Females				
	0	10	40	200	1500	0	10	40	200	1500
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Centrilobular hepatocellular vacuolization	0	0	2	2	29	1	1	1	6	32
Centrilobular hepatocellular enlargement	0	0	0	1	46	0	0	0	0	49
Inflammation, chronic	28	11	9	11	24	12	13	11	9	13
Bile duct, hyperplasia	42	43	43	44	44	38	43	38	37	48
Bile duct, inflammation, chronic	44	46	47	43	47	39	44	40	36	39
Bile duct fibrosis	9	2	15	5	8	9	9	7	4	7
Foci of vacuolated hepatocytes	10	10	8	6	9	2	3	7	3	0
Cellular alteration, basophilic	14	18	11	20	16	21	15	21	19	20
Cellular alteration, clear/eosinophilic	20	23	15	29	25	16	9	16	16	30
Testes	(50)	(23)	(33)	(32)	(50)	(0)	(0)	(0)	(0)	(0)
Hypospermatogenesis, bilateral	2	2	5	3	7	0	0	0	0	0
Arteritis/periarteritis	7	4	2	4	9	0	0	0	0	0
Interstitial cell hyperplasia	10	3	2	7	11	0	0	0	0	0

E. Other Relevant Toxicology Information

1. Mutagenicity

Uniconazole was negative for bacterial gene mutation in Salmonella typhimurium when tested up to cytotoxic levels with metabolic activation, and up to solubility levels without metabolic activation. Uniconazole gave negative responses in E. coli with and without metabolic activation.

Uniconazole was also negative for chromosomal aberrations in cultured Chinese hamster ovary cells when tested up to cytotoxic levels without metabolic activation, but was positive when tested with metabolic activation.

Uniconazole was positive in the mouse micronucleus assay when tested in male mice. Although no individual animal data for males and no data on female mice were presented in the study report, this does not preclude the use of the positive response observed in males as part of the weight of the evidence determination.

Uniconazole did not appear to induce unscheduled DNA synthesis in rat hepatocytes when tested by the in vivo/in vitro technique. This study was not originally considered acceptable, by the reviewer, for regulatory purposes since duplicate cultures from each animal were not prepared and that a small number of animals used per dosing situation. However, in a subsequent consideration (K. Dearfield, 7/25/90), justification was made to upgrade the study to be acceptable.

Based on this evidence, it is recommended that additional testing be performed to address the mutagenicity concern. Based on the positive results for aberration and micronucleus induction, a rodent dominant lethal assay is necessary to further assess the potential of uniconazole to induce genetic effects in germ cells.

2. Metabolism

When male and female rats were dosed with ^{14}C-Uniconazole, either in single or repeated doses, it was rapidly absorbed, extensively metabolized, and rapidly excreted. Peak tissue (including plasma) concentrations of radioactivity occurred 1 to 8 hours

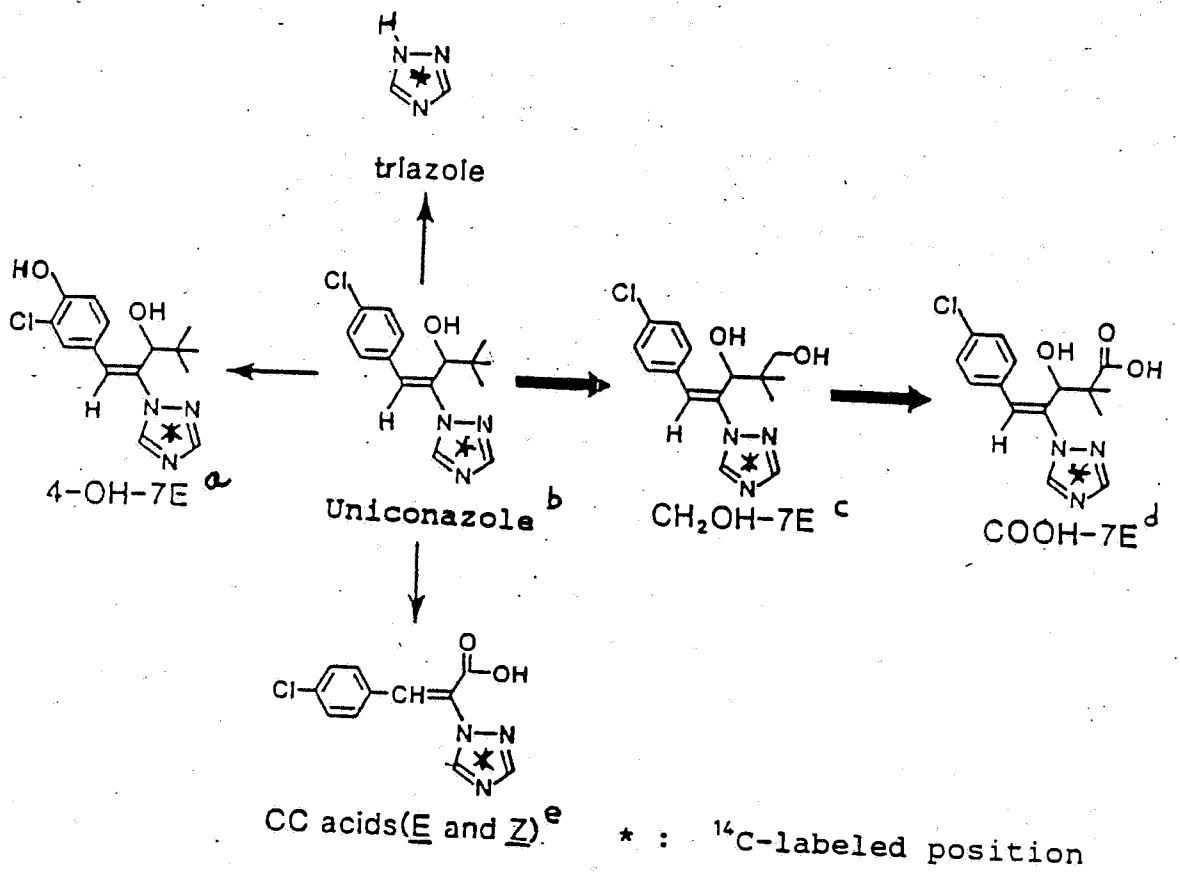


Figure 1. Proposed Metabolic Pathways for Uniconazole in Rats

a (S)-(E)-1-(p-chloro-4-hydroxyphenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-1-penten-3-ol [designated as 4-OH-7E]

b (S)-(E)-1-(p-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-1-penten-3-ol [uniconazole]

c (S)-(E)-1-(p-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-1-penten-1,3-diol [designated as CH_2OH-7E]

d (S)-(E)-1-(p-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-1-pentenoic acid [designated as COOH-7E]

e (E)- and (Z)-alpha-(1,2,4-triazol-1-yl)-p-chlorocinnamic acid [designated as CC acids (E) and (Z)]

after administration of a single low dose. Ninety-six to 99 percent was excreted within 3 days. The radioactivity recovered in urine, feces, and CO_2 in exhaled air was 40 to 66, 33 to 59, and 0.1 percent of the administered dose, respectively. Five metabolites were identified in the urine and feces. These represent 83 to 91 percent of the administered dose. The major metabolites of Uniconazole were two oxidation products (58-75 percent of the dose) of the tert-butyl group and a free triazole (3-15 percent of the dose) liberated from Uniconazole. The proposed metabolic pathway for Uniconazole is shown in Figure 1.

3. Acute, Subchronic, and Chronic Effects

The acute oral LD_{50} in rats was 460 mg/kg in male rats and 430 mg/kg in female rats when administered in corn oil. In PEG 10% and methylcellulose 1%, the acute oral LD_{50} was 2020 mg/kg in male rats and 1070 mg/kg in female rats.

A 90-day oral study in dogs was performed in which Uniconazole was administered via gelatin capsules at doses of 0, 5, 20, 80, and 320 mg/kg/day. Toxic effects noted in this study were: decreased food consumption and body weight, increased SGPT and BSP retention, increased liver weights, hepatocellular enlargement, and cytoplasmic vacuolation of hepatocytes in animals administered 20 mg/kg/day and above.

A 1-year dog study was performed at doses of 0, 2, 20, and 200 mg/kg/day administered via gelatin capsules. There was no effect of dosing on mortality. Mean body weight gains were significantly reduced in highdose males and females at weeks 0 to 4, and in highdose males at weeks 0 to 52. Mean food consumption was similar in all dose groups. Alkaline phosphatase activity was significantly elevated in both sexes receiving 200 mg/kg/day and was considered treatment-related. SGPT also was elevated in some high-dose dogs. Absolute and relative (to body weight) liver weights were significantly increased in male and female dogs receiving 200 mg/kg/day and in male dogs receiving 20 mg/kg/day. There were no gross morphological changes in the test animals which could be attributed to compound administration. Changes in the liver weights of high-dose animals corresponded

with histological changes in the liver, including hepatocellular enlargement with increased cytoplasmic homogeneity and increased bile pigment. The NOEL was 2 mg/kg/day and the LOEL was 20 mg/kg/day based on the increased liver weights observed at the 20 mg/kg dose.

4. Developmental and Reproductive Effects

When Technical Uniconazole was administered to pregnant New Zealand White rabbits at doses of 0, 1, 3, 10, and 20 mg/kg from day 7 through 19 of pregnancy, the chemical did not produce any adverse effects on pregnancy rates, number of corpora lutea, implantation sites, resorption, live fetuses, fetuses/dam, mean fetal weight, or sex ratio in the offspring. In addition, administration of Uniconazole did not result in increases in external, visceral, or skeletal abnormalities. Food consumption was reduced significantly, and body weight gain was marginally reduced in does administered 20 mg/kg/day. The NOEL for maternal toxicity was 10 mg/kg. The NOEL for developmental toxicity was 20 mg/kg/day.

A rat teratology study was performed in Scl:SD rats by gavage at doses of 0, 1, 5, 25, and 50 mg/kg/day from day 6 through 15 of pregnancy. Administration of the compound resulted in decreased maternal body weight gain at doses of 25 mg/kg and above. Administration of the test compound was associated with an increased incidence of 14th rib in offspring of dams administered 25 mg/kg and above. The study was considered Core-Supplementary.

A two-generation reproduction study was conducted in rats at doses of 0, 15, 150, and 1500 ppm in the diet. Adverse effects observed among F_0 and F_1 parental animals were: reduced body weight, food consumption, increased liver weight, hepatocellular enlargement, and vacuolization at 1500 ppm. Fertility was unaffected, as was gestation time, by ingestion of the test compound in the diet. Pup weights were adversely affected at the highest dose level. The NOEL was 150 ppm (equivalent to 7.5 mg/kg/day).

5. Structure-Activity Relationship

Uniconazole is structurally related to other triazole pesticides such as triadimefon (Bayleton), triadimenol (Baytan), propiconazole (Tilt), terbuconazole

(Folicur), etaconazole (Sonax, Vanguard), bitertanol (Baycor), cyproconazole (SAN 619F), azaconazole, and hexaconazole (Anvil). Figure 1 shows the chemical structures of these chemicals.

Triadimenol, a primary metabolite of Bayleton, was classified by the HED Peer Review Committee as a Group C, possible human carcinogen based on increased incidences of liver adenomas in female CFI-W74 mice (HED Report dated January 29, 1988). This classification was upheld by the FIFRA Scientific Advisory Panel in their meeting of December 1978 (report dated December 23, 1987).

Propiconazole was associated with increased incidences of hepatocellular adenomas and carcinomas in male CD-1 mice, and was classified by the HED Peer Review Committee in Group C, possible human carcinogen (HED reports dated April 29, 1987, July 21, 1988, April 28, 1989, and January 22, 1990).

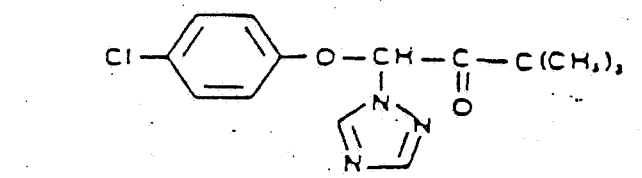
Etaconazole was associated with increased incidences of liver adenomas and carcinomas in both male and female Albino Swiss mice. However, the registration application was voluntarily withdrawn and no further action was taken regarding its cancer classification.

Cyproconazole was associated with statistically significant increases in the incidence of hepatocellular adenomas and carcinomas in male and female CD-1 mice, and was classified as a Group C, possible human carcinogen, by the HED Peer Review Committee on June 20, 1990.

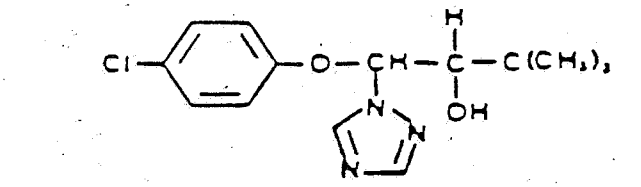
Bitertanole and azaconazole were reported to be negative for carcinogenicity in mice when administered in the diet at doses up to 500 ppm. Terbuconazole and hexaconazole were reported to be negative for carcinogenicity in mice when administered in the diet up to 180 and 200 ppm, respectively. However, all other triazole chemicals, except for Cyproconazole which has somewhat different structure, were tested up to 1500 ppm or higher before inducing any carcinogenic response in mice.

Hexaconazole was associated with an increased incidence of benign Leydig cell tumors in rat testes, and was classified by the HED Peer Review Committee as a Group C carcinogen on June 27, 1990.

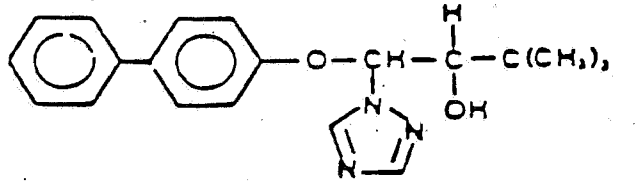
Administration of Bayleton was associated with increased incidences of liver adenomas in both sexes of B6C3F1 mice. The chemical was classified as a Group C carcinogen on June 27, 1990.



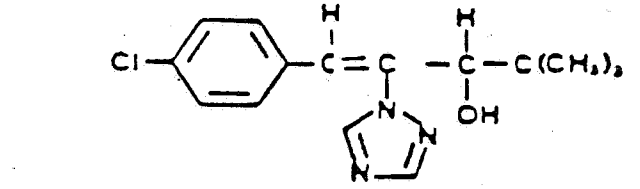
Triadimefon
(Bayleton)



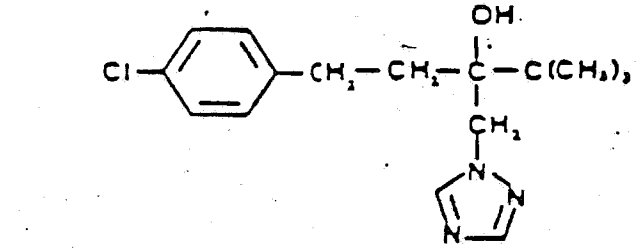
Triadimenol
(Baytan)



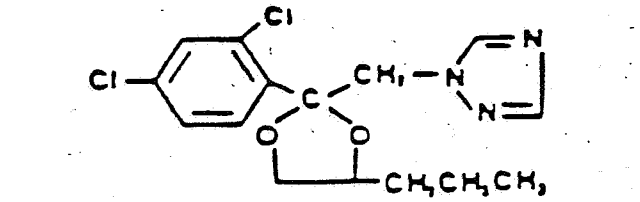
Bitertanol
(Baycor)



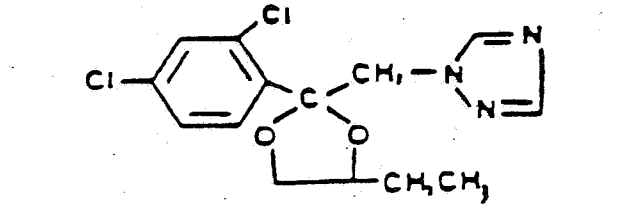
Uniconazole
(Prunit)



Terbuconazol
(Folicur)

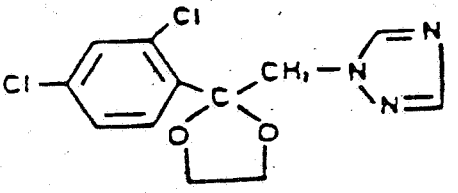


Propiconazole
(Tilt)

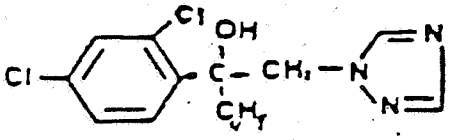


Etaconazole
(Vangard)

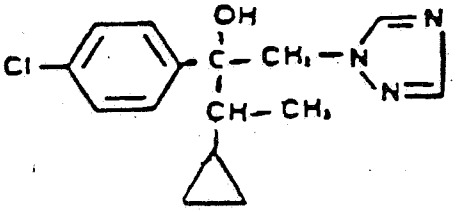
Figure 2. Uniconazole and Structurally-Related Chemicals



Azaconazole



Hexaconazole
(Anvil)



Cyproconazole
(SAN 619F)

Figure 2a. Uniconazole and Structurally-Related Chemicals

Among all triazole pesticides reviewed by the HED Peer Review Committee, hexaconazole was the only chemical to induce carcinogenic response in rats in a form of benign Leydig cell tumor in testes. Other triazoles were either negative or were not tested at adequete dose levels in the rat studies.

Among all triazole pesticides reviewed by the HED Peer Review Committee, only one chemical other than Uniconazole, i. e. Cyproconazole, was reported to have potential to induce mutagenic response. Cyproconazole was positive for potential to induce chromosomal aberrations in CHO cells with and without metabolic activation. The chemical was negative in micronucleus assay in mice, for gene mutation in the Salmonella assay, and for cell transformation with Syrian hamster embryo cells with and without metabolic activation. However, Cyproconazole has a somewhat slightly different structure than other triazole pesticides, in that it has a cyclopropane moiety that is unique to Cyproconazole.

Both Bayleton and bitertanol were reported to produce cleft palates in rat offspring when the dams were administered the test compound during gestation. Cyproconazole and Baytan were reported to be associated with increased incidences of supernumerary ribs in rats when administered to pregnant females during gestation. It is recommended that this class of compounds should be examined in detail for developmental and reproductive effects.

F. Weight-of-the-Evidence Considerations

The Committee considered the following facts regarding the toxicology data on Uniconazole to be of importance in a weight-of-the-evidence determination of carcinogenic potential.

1. Dietary administration of Uniconazole to CD-1 male mice was associated with statistically significant increases in hepatocellular adenomas, carcinomas, and adenomas/carcinomas combined when compared to controls, with increasing positive trends. The incidences of hepatocellular adenomas were outside the historical control incidence for this type of lesion in CD-1 mice, but the incidence of carcinomas ~~were~~ was within the range of the historical control for this lesion in this strain of mice. The incidence of hepatocellular tumors in females was comparable to controls.

2. The high dose tested was considered adequate for a carcinogenicity bioassay, but it appears that females could have tolerated higher dosages.

3. The test chemical did not alter the spontaneous tumor profile in Crl:CD(BR)SD rats when tested up to 1000 ppm for 2 years.

4. Uniconazole did not induce a mutagenic response when tested in gene mutation systems using Salmonella typhimurium and E. coli with and without metabolic activation.

   Uniconazole was also negative for chromosomal aberrations when tested up to cytotoxic levels without metabolic activation, but was positive when tested with metabolic activation.

   Uniconazole was positive in the mouse micronucleus assay when tested in male mice. The data evaluation records indicated that the Agency had requested the submission of individual animal data for males. The test was not performed on females.

   Uniconazole did not appear to induce unscheduled DNA synthesis in primary mouse hepatocytes when tested in vivo/in vitro. The data evaluation records indicated that originally this study was not considered acceptable for regulatory purposes since duplicate cultures from each animal were not performed, and that a small number of animals was used in each dosing situation. However, a subsequent consideration (K. Dearfield, 7/25/90) provided adequate justification to upgrade the study to an acceptable level.

   Based on the positive clastogenicity responses, a rodent dominant lethal assay is recommended to be performed with uniconazole.

5. Uniconazole is structurally similar to other triazole pesticides, most of which induce hepatocellular carcinomas and/or adenomas in one or both sexes of mice.

G. Classification

Considering criteria contained in EPA Guidelines [FR 51:33992-34003, 1986] for classifying a carcinogen, the Committee concluded that Uniconazole should be classified as Group C, possible human carcinogen.

This classification was based upon statistically significant increases in hepatocellular adenomas, carcinomas, and adenomas/carcinomas combined, with a positive dose trend. The incidence of adenomas were outside the historical control range, and the incidence of carcinomas were within the historical control range for these types of lesions in this strain of mice.

This classification was supported by the structural similarity of Uniconazole to other carcinogenic triazole pesticides, most of which have the potential to induce hepatocellular tumors in one or both sexes of mice. This classification was further supported by positive genotoxic responses in several mutagenicity testing systems.

Quantification of potential human cancer risk, using a low dose extrapolation model ($Q1^*$), was not recommended. Therefore, the Reference Dose (RfD) approach will be employed for the quantification of human risk.

This decision was based on the fact that the tumor induced is primarily of benign nature, occurred at the highest dose tested in one sex of one species with no acceleration in rate, and finally, the tumor did not exhibit any uncommon biological behavior.